MEMORANDUM

SUBJECT: Consideration of Eligibility for Registration of
the New Pesticide Active Ingredient
Polyoxin D Zinc Salt
-DECISION MEMORANDUM-

FROM: Janet L. Andersen, Director
Biopesticides and Pollution Prevention Division (7511W)

TO: Daniel M. Barolo, Director
Office of Pesticide Programs (7501C)

ISSUE

Should the Agency grant registration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) § 3(c)(5) for the technical product and the end-use product containing the new biochemical-like active ingredient, polyoxin D zinc salt (PC Code 230000), for use on turf sites including golf courses, home lawns, parks and commercial and institutional grounds for control of Brown Patch and Large Patch disease caused by *Rhizoctonia solani?*

CONCLUSION

Data requirements for granting these registrations under Section 3(c)(5) of FIFRA have been fulfilled. Available and submitted data have been reviewed and the Biopesticides and Pollution Prevention Division (BPPD) has made a determination of reasonable certainty of no harm to humans, especially infants and children, and the environment from the use of this active ingredient. BPPD recommends unconditional registration.

BASES FOR CONCLUSION

A. DATA GAPS

There are no data gaps. There exists a potential risk to aquatic species. However, exposure to aquatic species is considered minimal to negligible when the end-use product containing the active ingredient is used according to label instructions.

B. SUMMARY OF FINDINGS

(1) Product Identity

Polyoxin D Zinc Salt Technical and the end-use product, STOPIT™ Wettable Powder Turf Fungicide (EPA File Symbols 068173-R and 068173-E, respectively), are the first products containing the biochemical-like active ingredient polyoxin D zinc salt (PC Code 230000).

Polyoxin D (also known as polyoxorim), the active portion of the polyoxin D zinc salt compound, is an antibiotic and acts to inhibit the growth of phytopathogenic fungal cell wall chitin by competitively inhibiting chitin synthetase. Polyoxin D is produced via a fermentation process using *Streptomyces cacaoi* var. asoensis, which was isolated from a soil sample collected in Japan. Polyoxin D is very water soluble so it is formulated as the zinc salt to give longer residence time on plant surfaces. The compound is fungistatic and reportedly has no residual effects after the compound has degraded or washed off surfaces.

The technical product, Polyoxin D Zinc Salt Technical, is used for the manufacture of the end-use product. The end-use product, STOPIT™ Wettable Powder Turf Fungicide, contains 2.5% polyoxin D zinc salt.

(2) Use Sites/Usage

The proposed end-use involves ground and hand spray foliar applications of wettable powder to turf sites including golf courses, home lawns, parks and commercial and institutional grounds. STOPIT™ Wettable Powder Turf Fungicide is not for use on turf being grown 1) for sale or other commercial use as sod, 2) for commercial seed production, or 3) for research purposes.

(3) Human Health Risk Assessment

(a) Toxicological Endpoints

No toxicological endpoints were identified. No unreasonable adverse human health effects were identified.

(b) Human Exposure

All data requirements have been fulfilled for the active ingredient. No numeric tolerance or exemption from the requirement of a tolerance is needed since polyoxin D zinc salt will not be registered for uses on food.

The acute oral toxicity studies, acute inhalation studies and primary dermal

irritation studies indicated Toxicity Category IV for both Polyoxin D Zinc Salt Technical and STOPIT™ Wettable Powder Turf Fungicide. The acute dermal toxicity studies indicated Toxicity Category III for Polyoxin D Zinc Salt Technical and for STOPIT™ Wettable Powder Turf Fungicide. The primary eye irritation study indicated Toxicity Category III for polyoxin D zinc salt and for STOPIT™ Wettable Powder Turf Fungicide. The hypersensitivity study indicated polyoxin Z zinc salt was a mild sensitizer at a 5% dose, and that the end-use product was a non-sensitizer. To date, there have been no hypersensitivy incidents reported in handlers of the technical or end-use product.

(c) Risk Assessment

The battery of acute and chronic toxicological studies indicates polyoxin D zinc salt induces minimal toxic affects to humans through oral, dermal, ocular or inhalation exposure. We have also considered polyoxin D zinc salt in light of the nine safety factors listed in the Food Quality Protection Act (FQPA) and have made a determination of reasonable certainty of no harm. In short, BPPD has not identified any subchronic, chronic, immune, endocrine, or non-dietary cumulative exposure issues as they may affect infants and children and the general population.

(4) Ecological Risk Assessment

(a) Ecological Toxicity Endpoints

No unreasonable adverse ecological or environmental fate effects on avian, aquatic or other nontarget organisms were identified.

(b) Ecological Exposure

Potential exposure to freshwater invertebrates and fish, via runoff after application, will be minimized by mitigating Environmental Hazards label text.

(C) Risk Assessment

Ecological effects studies were performed on mallard duck, freshwater invertebrates and rainbow trout and non-target insects including two-spotted spider mites, brown plant hoppers, and diamond back moths. Toxicological studies indicated that there is no significant toxicity to rodents from acute oral testing at the maximum hazard dose. Therefore, risk to mammalian wildlife is expected to be minimal to nonexistent. Polyoxin D zinc salt was found to be practically non-toxic to the mallard duck, which is a representative species for avian risk assessment. Based on the results of the non-target insect study, exposure to polyoxin D zinc salt is not expected to pose significant increased risks to terrestrial insects. In the studies submitted, moderate toxicity to aquatic species (freshwater invertebrates and rainbow trout) was observed. No unreasonable adverse ecological or environmental fate effects were identified by the duck, mite and insect testing. Potential exposure to freshwater invertebrates and fish will be minimized by appropriate precautionary labeling.

OFFICE DIRECTOR CONCURRENCE

The Biopesticides and Pollution Prevention Division (BPPD) recommends that the biochemical-like pesticide technical and end-use products containing the new active ingredient polyoxin D zinc salt be unconditionally registered under 3(c)(5) of FIFRA for the specified terrestrial non-food turf use sites including golf courses, home lawns,

parks, commercial and institutional grounds for control of Brown Patch and Large Patch disease caused by *Rhizoctonia solani.*

Concurrence: _____

Non Concurrence: _____

Date: _____

Polyoxin D Zinc Salt
(PC Code 230000)

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I. Executive Summary

A. IDENTITY

The Agency has classified polyoxin D zinc salt as a biochemical-like pesticide. Polyoxin D, the active portion of the polyoxin D zinc salt compound [zinc 5-[[2-amino-5-O-(aminocarbonyl)-2-deoxy-L-xylonoyl]amino]-1-(5-carboxy-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl)-1,5-dideoxy-β-D-allofuranuronate], is produced via a fermentation process using *Streptomyces cacaoi* var. asoensis, which was isolated from a soil sample collected in Japan. Polyoxin D (also known as polyoxorim) is an antibiotic and acts to inhibit the growth of phytopathogenic fungal cell wall chitin by competitively inhibiting chitin synthetase. Polyoxin D is very water soluble, so it is formulated as the zinc salt to give longer residence time on plant surfaces. The compound is fungistatic and reportedly has no residual effects after the compound has degraded or washed off surfaces.

The technical product, Polyoxin D Zinc Salt Technical, is used for the manufacture of the end-use product. The end-use product, STOPIT™ Wettable Powder Turf Fungicide, contains 2.5% polyoxin D zinc salt.

B. USE/USAGE

The proposed end-use involves ground and hand spray foliar applications of the wettable powder formulation to turf sites.

C. RISK ASSESSMENT

There is a reasonable certainty that no harm will result from aggregate exposure to the active ingredient polyoxin D zinc salt. This includes all anticipated dietary exposures and all other exposures for which there is reliable information.

1. Human Health Risk Assessment

a. Toxicological Endpoint

No toxicological endpoints were identified.

b. Human Exposure

Mammalian toxicology data have been submitted and adequately satisfy data requirements to support the registration. The acute dermal and primary eye toxicity tests submitted using polyoxin D zinc salt and using the end-use product STOPIT™ Wettable Powder Turf Fungicide all resulted in Toxicity Category III classification. Other toxicity tests submitted (the acute oral, acute inhalation, and primary dermal irritation tests) using both the technical grade active ingredient and the end-use product resulted in Toxicity Category IV. Results of hypersensitivity studies indicated the technical grade active ingredient was a mild sensitizer and the end-use product was a non-sensitizer. In addition, the registrant submitted results of chronic exposure and oncogenicity studies indicating Polyoxin D Zinc salt did not produce significant toxic or oncogenic responses in mice or rats after dietary exposure at various doses for a 24 month period.

c. Risk Assessment

Polyoxin D zinc salt has been considered in light of the nine safety factors listed in the Food Quality Protection Act (FQPA) and a determination of reasonable certainty of no harm has been made. In short, BPPD has not identified any subchronic, chronic, immune, endocrine, or nondietary cumulative exposure issues that might affect infants and children or the general population.

2. Ecological Risk Assessment

a. Ecological Toxicity Endpoint

Ecological effects studies were performed on mallard duck, freshwater invertebrates, rainbow trout and non-target insects including two-spotted spider mites, brown plant hoppers, and diamond back moths.

No unreasonable adverse ecological or environmental fate effects on avian, aquatic or other nontarget organisms were identified.

b. Ecological Exposure

Data waivers were granted for non-target plants and honeybee toxicity studies based on the limited turf only application sites and expected minimal exposure to pollinating insects, i.e. honeybees. In the studies submitted, moderate toxicity to aquatic species (freshwater invertebrates and rainbow trout) was the only observed toxicity. Exposure to daphnids, other aquatic invertebrates and fish could occur based on current label use directions, however, the acute risk to aquatic organisms will be minimized via mitigating label language.

c. Risk Assessment

Non-target organism toxicity studies, in conjunction with exposure considerations for the use pattern, indicate no unreasonable adverse effects.

D. DATA GAPS/LABELING RESTRICTIONS

There are no data gaps. There exists a potential risk to aquatic species. However, exposure and therefore risk to aquatic species is considered minimal to negligible when the end-use product containing the active ingredient is used in accordance with the limitations specified in the label.

II. OVERVIEW

A. ACTIVE INGREDIENT OVERVIEW

Common Name: Polyoxin D Zinc Salt

Chemical Name: zinc 5-[[2-amino-5-O-(aminocarbonyl)-2-deoxy-L-xylonoyl]amino]-1-(5-carboxy-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl)-1,5-dideoxy-β-D-allofuranuronate

Chemical Family: Polyoxins - agricultural antifungal antibiotic complex

CAS Registry Number: 146659-78-1 (1:1 zinc salt)
22976-86-9 (polyoxin D, or polyoxorim)

OPP Chemical Code: 230000 Polyoxin D Zinc Salt

Empirical Formula: $C_{17}H_{21}N_5O_{14}$. Zn (1:1 zinc salt)
$C_{17}H_{23}N_5O_{14}$

Trade and Other Names: Polyoxin D Zinc Salt Technical
STOPIT™ Wettable Powder Turf Fungicide

Basic Manufacturer: Kaken Pharmaceutical Co., Ltd.
Agrochemicals and Animal Health
Products Division
3-4-10, Nihonbashi Honcho
Chuo-ku, Tokyo 103, Japan

B. USE PROFILE

The following is information on the proposed uses with an overview of use sites and application methods.

Type of Pesticide: Biochemical-like pesticide, a phytopathogenic fungal wall chitin synthetase inhibitor

Use Sites: The end-use product, STOPIT™ Wettable Powder Turf Fungicide, is for use on turf sites including golf courses, home lawns, parks and commercial and institutional grounds. It is not for use on turf being grown 1) for sale or other commercial use as sod, 2) for commercial seed production, or 3) for research purposes.

Target Pests: *Rhizoctonia solani*, the causative agent of Brown Patch or Large Patch disease

Formulation Types: The technical grade product, Polyoxin D Zinc Salt Technical, is a powder. The end-use product, STOPIT™ Wettable Powder Turf Fungicide, is a wettable powder.

Method and Rates of Application: 0.006 lb ai/1000 ft^2 (117 g ai/acre) in a minimum of 0.5 gallons of water per 1000 ft^2 (21.8 gpa).

Treatment should be repeated on a 7-14 day schedule as necessary when environmental conditions are conducive to development of disease. The shorter

interval should be used when disease symptoms are present.

Type of Treatment: foliar spray

Equipment: ground-based sprayer

Use Practice Limitations: Do not use STOPIT™ Wettable Powder Turf Fungicide through any type of irrigation system.

C. ESTIMATED USAGE

None used yet since these will be the first registered products.

D. DATA REQUIREMENTS

For polyoxin D zinc salt, the mammalian toxicology data requirements for the technical product have been fulfilled. Product analysis data requirements are adequately satisfied. All ecological effects data requirements for polyoxin D zinc salt have been adequately fulfilled. The data requirements for granting this registration under Section 3(c)(5) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) have been reviewed by the Biopesticides and Pollution Prevention Division (BPPD). Based on available information, the Agency foresees no unreasonable adverse effects to human health and the environment from the use of this biochemical-like pesticide.

E. REGULATORY HISTORY

Kaken Pharmaceutical Company, Ltd., represented by Stewart Pesticide Registration Associates, Inc., submitted applications for registration of Polyoxin D Zinc Salt Technical and the end-use product STOPIT™ Wettable Powder Turf Fungicide to the Registration Division on May 26, 1994. The application was subsequently transferred to the Biopesticides and Pollution Prevention Division (BPPD) to be considered as a "biochemical-like" substance for registration. Polyoxin D zinc salt was classified by BPPD as a "gray area pesticide" on May 16, 1995. The receipt of the applications for registration was published in the **Federal Register** on September 27, 1995, (60 FR 49838). There were no comments received in response to the notice of application.

F. FOOD CLEARANCES/TOLERANCES

A numeric tolerance or exemption from the requirement of a tolerance is not required for polyoxin D zinc salt since there are no food uses associated with the registration. Safety factors from the Food Quality Protection Act of 1996 (FQPA) were considered.

III. Science Assessment

A. PHYSICAL/CHEMICAL PROPERTIES ASSESSMENT

All product chemistry data requirements for polyoxin D zinc salt technical grade active ingredient are satisfied. These data support a registration eligibility decision.

1. Product Identity

Polyoxin D (also known as polyoxorim), the active portion of the polyoxin D zinc salt compound (zinc 5-[[2-amino-5-O-(aminocarbonyl)-2-deoxy-L-xylonoyl]amino]-1-(5-carboxy-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl)-1,5-dideoxy-β-D-allofuranuronate), is produced via a fermentation process using *Streptomyces cacaoi* var. asoensis, which was isolated from a soil sample collected in Japan. Polyoxin D is very water soluble, so it is formulated as the zinc salt to give longer residence time on plant surfaces. The compound is fungistatic and reportedly has no residual effects after the compound has degraded or washed off surfaces.

Mode of Action: Polyoxin D is an antibiotic and acts to inhibit the growth of phytopathogenic fungal cell wall by competitively inhibiting chitin synthetase.

2. Food Clearances/Tolerances

Polyoxin D zinc salt is a fungicide intended for turf uses only. Therefore, a numeric tolerance or exemption from the requirement of a tolerance is not an issue for these non-food uses.

Safety factors from FQPA were evaluated. BPPD has considered, among other relevant factors, available information concerning the aggregate exposure levels of consumers (and major identifiable subgroups of consumers) to the pesticide residue and exposure from non-occupational sources. Given the low toxicity of polyoxin D zinc salt as indicated by both the acute and chronic mammalian toxicity studies, a determination of reasonable certainty of no harm for the general population as well as subgroups including infants and children was made.

3. Physical and Chemical Properties Assessment

The generic data requirements for physical and chemical characteristics of the technical grade active ingredient are summarized in Table 1.

Table 1. Product Chemistry Data Requirements

Guideline no.	STUDY	RESULTS	MRID no.
151-10	Product Identity	polyoxin D is an agricultural antifungal antibiotic complex discovered in cultural broths of *Streptomyces cacaoi* var. asoensis ATCC 19093	432618-09, 4327618-10
151-11	Manufacturing Process	Technical manufactured by a batch fermentation process using *Streptomyces cacaoi* var. asoensis ATCC 19093	432618-09
151-12	Discussion of formation of unintentional ingredients	impurities were identified via HPLC/UV analytical method and microbiological assay	432618-09, 442498-01
151-13	Analysis of Samples	X-ray diffraction analysis was used to identify impurities	432618-11, 442497-01
151-15	Certification of Limits	Limits listed in the CSF are adequate	CSF, 442497-01
151-16	Analytical Method	HPLC/UV analytical method and microbiological assay were used	432618-13, 432618-14, 432618-15
151-17	**Physical and Chemical Properties**	**Results, Method/MRID No. of Technical Grade Active Ingredient**	
	color	brown	Munsell/432618-16,17
	Physical State	powder	visual/432618-16, -17
	Odor	musty	432618-16, 17
	Melting Point	122.5 $\pm$ 0.1, decompose at 170° C	432618-16
	Density (20 - 27.1°C)	1.8392 g/cm^3, 2.32441 g/cm^3	gas pycnometer/432618-16, -17
	Solubility: (g/100 ml)	solvents: at 25° C water 1.0, methanol,* octanol*	432618-16
	Dissociation Constant	3.25, 4.16, 8.0, 9.56, and 10.5	pH meter/432618-16
	pH (23.2°C)	1% solution = 7.51 6.9 (6.7 - 7.2)	pH meter/432618-16 pH meter/432618-18
	Stability	stable at 0 and 12°C (96 hrs); complete degradation (95.8%) at 54°C for 14 days; no change to metals zinc and iron foil; unstable in sunlight 39.3% degradation in 24 hrs	432618-19
	Storage Stability	100% up to 12 months, slightly decreased 3% during 24 months, and in 4 yrs decreased about 5%	HPLC/432618-21

* The solubility in organic solvents was not reliable and changed with time. Therefore, octanol/water partition coefficient was not performed.

B. HUMAN HEALTH ASSESSMENT

Mammalian toxicology data have been submitted and adequately satisfy the requirements as set forth in 40 CFR 158.690 for biochemical pesticides for non-food, domestic outdoor uses.

1. Toxicology Assessment

Adequate mammalian toxicology data are available to support registration of the active ingredient polyoxin D zinc salt.

a. Acute Toxicology

The following toxicity studies were submitted for registration of polyoxin D zinc salt technical grade active ingredient and are acceptable for purposes of registration.

Table 2. Mammalian Toxicity Studies with Polyoxin D Zinc Salt

Guideline No.	Study	Results	Toxicity Category	MRID No.
152-10	Acute Oral LD_{50} (rat)	male: > 15,000 mg/Kg bodyweight female: 10,000 to 15,000 mg/Kg bodyweight	IV	432618-23
152-11	Acute Dermal LD_{50} (rat)	> 2,000 mg/Kg bodyweight	III	432618-25
152-12	Acute Inhalation LC_{50} (rat)	> 2.44 mg/L for males > 2.17 mg/L for females	IV	432618-27
152-13	Primary Eye Irritation (rabbit)	slight to moderate irritation (Draize)	III	432618-29
152-14	Primary Dermal Irritation (rabbit)	slight irritation (Draize)	IV	432618-31
152-15	Hypersensitivity Study (guinea pigs)	mild sensitizer at 5% TGAI (GPMT)	N/A	432618-33
152-16	Hypersensitivity Incidents	none reported	N/A	N/A

The following studies were submitted in fulfillment of requirements for registration of the end-use product STOPIT™ Wettable Powder Turf Fungicide and are acceptable for purposes of registration.

Table 3. Mammalian Toxicity Studies with STOPIT™ Wettable Powder Turf Fungicide

Guideline No.	Study	Results	Category	MRID No.
152-10	Acute Oral LD_{50} (rat)	> 5,000 mg/Kg bodyweight	IV	432618-24
152-11	Acute Dermal LD_{50} (rat)	> 2,000 mg/Kg bodyweight	III	432618-26
152-12	Acute Inhalation LC_{50} (rat)	> 4.93 mg/L for males and females combined	IV	432618-28

152-13	Primary Eye Irritation (rabbit)	mild irritation (Draize)	III	432618-30
152-14	Primary Dermal Irritation (rabbit)	non-irritant (Draize)	IV	432618-32
152-15	Hypersensitivity Study (guinea pigs)	non-sensitizer (modified Buehler method)	N/A	432618-34
152-16	Hypersensitivity Incidents	none reported	N/A	N/A

b. Mutagenicity and Developmental Toxicity

Genotoxicity studies are conditionally required to support non-food uses only if the use is likely to result in significant human exposure, or the active ingredient or its metabolites are structurally related to a known mutagen, or the active ingredient belongs to any chemical class of compounds containing known mutagens. Although the triggers for genotoxicity studies were not met by polyoxin D zinc salt, the registrant submitted mutagenicity and developmental toxicity studies to support registration.

Results of the mutagenicity studies indicated Polyoxin D Zinc Salt Technical was weakly mutagenic in an Ames Assay (MRID # 433230-01) and not mutagenic in a host mediated assay (MRID # 432618-36). If a food/feed use is ever sought, the test results will require a review of the mutagenicity data base to determine the need for additional studies. However, for this registration, since polyoxin D zinc salt is to be used solely as a turf fungicide, the mutagenicity question is not an issue and the data base is acceptable to support registration.

No maternal toxicity or developmental toxicity was observed at any dose in the developmental toxicity study, MRID # 432618-37.

Table 4. Mutagenicity and Developmental Toxicity Studies

Guideline No.	**Study**	**Results**	**MRID No.**
152-17	Ames Test	weakly mutagenic*	433230-01
152-19	Three Mutagenicity Tests		432618-36
	a. REC-Assay with *B. subtilis* H-17 and M-45	unacceptable **	"
	b. Ames Test	unacceptable **	"
	c. Host-mediated Assay (mice)	not mutagenic ***	"

152-23	Developmental Toxicity	maternal NOEL = 50 mg/Kg/day polyoxin D zinc salt****; maternal LOEL = 50 mg/Kg/day polyoxin D zinc salt; developmental toxicity NOEL is > 800 mg/Kg/day polyoxin D zinc salt	432618-37

* in two separate assays, a comparison of the revertant colonies in the test groups with those treated with positive control chemicals indicates that the test substance is only weakly positive
** these studies were classified as unacceptable due to lack of pertinent detail and data or for protocol deficiencies
*** this study is no longer used to satisfy requirements for gene mutation study, however, it can be used to support the negative conclusions of MRID # 433230-01
**** maternal NOEL based on decreased body weight; developmental toxicity studies based on polyoxin D zinc salt (25.7 - 26.1 % active ingredient)

c. Subchronic Assessment Tests

A 90-day feeding study is not required because the non-food non-feed uses do not require a numeric tolerance or an exemption from the requirement of a tolerance; and the uses are not likely to result in repeated human exposure by the oral route. Likewise, the 90-day dermal and inhalation toxicity studies are not required because the use pattern does not result in a long-term inhalation exposure at concentrations that are likely to be toxic, and there is no purposeful application to human skin, nor is prolonged dermal exposure likely.

d. Chronic Exposure and Oncogenicity Assessment

Chronic exposure studies are conditionally required to support non-food uses only if the potential for adverse chronic effects are indicated based on 1) the subchronic effect levels established in the Tier I subchronic oral toxicity, subchronic dermal or subchronic inhalation, 2) the pesticide use pattern or 3) the frequency and level of repeated human exposure that is expected. Oncogenicity studies are required to support non-food uses only if 1) the active ingredient or any of its metabolites, degradation products or impurities produce in Tier I studies morphologic effects in any organ that potentially could lead to neoplastic change. Although the triggers for chronic exposure and oncogenicity studies were not met by polyoxin D zinc salt, the registrant submitted results of a chronic exposure study and an oncogenicity study to support registration.

Results of the chronic toxicity/oncogenicity studies indicated Polyoxin D Zinc Salt Technical did not produce significant toxic or oncogenic responses after mice were fed polyoxin D zinc salt at 0, 0.04%, 0.4% and 4% dose levels, beginning when the mice were six weeks old, and continuing for 24 months (MRID 432618-38). Furthermore, no significant toxic or oncogenic responses in rats were found after daily administration of polyoxin D zinc salt at 0, 0.01%. 0.1% 1.0% and 5% dose levels beginning when the rats were seven weeks old and continuing for 24 months (MRID 432618-39).

Table 5. Chronic Exposure and Oncogenicity Studies

Guideline No.	Study	Results	MRID No.
152-26/152-29	Chronic Exposure and Oncogenicity	NOEL = 3591 mg/Kg/day polyoxin D zinc salt in male mice and 4177 mg/Kg/day polyoxin D zinc salt in female mice	432618-38
152-26/152-29	Chronic Exposure and Oncogenicity	NOEL = 2058.7 mg/Kg/day in male rats and 2469.8 mg/Kg/day in female rats	432618-39

e. Effects on Immune and Endocrine Systems

The Agency is not requiring information on the endocrine effects of this biochemical pesticide at this time; Congress has allowed 3 years after August 3, 1996, for the Agency to implement a screening program with respect to endocrine effects. However, BPPD has considered, among other relevant factors, available information concerning whether the biochemical-like compound may have an effect in humans similar to an effect produced by a naturally occurring estrogen or other endocrine effects. The active ingredient, polyoxin D zinc salt, acts as a fungal chitin synthetase inhibitor. There is no known evidence so far that this compound acts as an endocrine disrupter in humans. Available developmental toxicity data do not indicate that polyoxin D zinc salt has any endocrine effects. Furthermore, results from chronic exposure and oncogenicity studies showed no significant toxic or oncogenic responses from polyoxin D zinc salt. Therefore, no adverse effects to the endocrine or immune systems are known or expected.

2. Dietary Exposure and Risk Characterization

The proposed use pattern for STOPIT™ Wettable Turf Fungicide, turf uses only, will not likely result in dietary exposure and does not require a numeric tolerance or an exemption from the requirement of a tolerance. Acute exposure could occur from small children ingesting treated turf foliage, or transferring residues from turf to hand to mouth, but would be very low because of the low application rates. In the absence of any toxicological endpoints, risk from the consumption of residues is not expected for both the general population and infants and children.

3. Occupational, Residential, School and Daycare Exposure and Risk Characterization

No indoor residential, school or daycare uses currently appear on the label. The proposed use pattern is for turf sites only. There is a potential for dermal exposure at these sites where children are present but the health risk is expected to be minimal to nonexistent based on evaluations of the submitted toxicological studies and the relatively low application rate.

a. Occupational Exposure and Risk Characterization

Based on the application methods, the potential for dermal, eye, and inhalation exposures to STOPIT™ Wettable Powder Turf Fungicide exists for applicators and handlers. However, because of the lack of significant mammalian acute and chronic toxicity, the specific mode of action as a fungal chitin synthetase inhibitor and the low use rates at 117 grams ai/acre, data on worker exposure (i.e. occupational exposure data) to the active ingredient are not required at this time. Risks from occupational exposure will be mitigated through the appropriate precautionary labeling.

b. Residential, School and Daycare Exposure and Risk Characterization

No indoor residential, school or daycare uses currently appear on the label. The proposed use pattern is for turf sites only. Non-dietary exposure at these sites could occur where children are present, but the health risk is expected to be minimal to nonexistent based on evaluations of the submitted studies and the low toxicity of polyoxin D zinc salt.

4. Drinking Water Exposure and Risk Characterization

Although the potential exists for a minimal amount of polyoxin D zinc salt to enter ground water or other drinking water sources if, after application, weather patterns are such that significant rainfall and surface water runoff occur, the health risk to humans is considered negligible based on the evaluations of the submitted toxicity studies, and the low application rate of the active ingredient.

5. Acute and Chronic Dietary Risks for Sensitive Subpopulations Particularly Infants and Children

There are no food uses associated with the registration of Polyoxin D Zinc Salt Technical and STOPIT™ Wettable Powder Turf Fungicide. Therefore, acute and chronic dietary risks should be minimal based on lack of exposure. Furthermore, results from mammalian acute and chronic toxicity studies indicate lack of toxicity, adding further weight to the lack of risk from exposure to polyoxin D zinc salt.

It is feasable that infants and children could incur minimal dietary exposure if, when they come into contact with recently treated turf, they either ingest treated turf foliage or transfer residues from turf to hand to mouth. However, the Agency has no information to indicate that children or infants would be more sensitive than adults to effects caused by polyoxin D zinc salt. Therefore, based on the lack of chronic and acute toxicity in the submitted studies, the potential risks to infants and children are considered negligible.

6. Aggregate Exposure from Multiple Routes Including Dermal, Oral, and Inhalation

Aggregate exposure would primarily occur in the mixer/loader/applicator subpopulation, via dermal and inhalation routes. Risks associated with dermal and inhalation aggregate exposure are measured via the acute toxicity studies submitted to support registration. Because the pulmonary studies for both the technical and end-use product showed no adverse effects (both Toxicity Category IV), the risks anticipated for this route of exposure are considered minimal. Results of the acute dermal studies using the

technical and using the end-use product indicated low toxicity (Toxicity Category III), and no significant dermal irritation (Toxicity Category IV). Based on these results, the anticipated risks from dermal exposure are also considered minimal. Therefore, the risks from aggregate exposure via dermal and inhalation exposure are a compilation of two low risk exposure scenarios and are considered negligible.

C. ENVIRONMENTAL ASSESSMENT

1. Ecological Effects Hazard Assessment

Ecological effects studies were performed on mallard duck, freshwater invertebrates, rainbow trout, and non-target insects including two-spotted spider mites, brown plant hoppers, and diamond back moths. In the studies submitted, moderate toxicity to aquatic species (freshwater invertebrates and rainbow trout) was observed. The freshwater invertebrates study, MRID # 432618-43 indicated that polyoxin D zinc salt was highly toxic to neonate (6 hour old) freshwater invertebrates, but showed no effects during a range finding test with 20 hour old freshwater invertebrates. The rainbow trout study indicated moderate toxicity to rainbow trout with a 96 hr LC_{50} of 5.06 ppm polyoxin D zinc salt. As a mitigation measure to protect aquatic species, the end-use product label will include the following statement under the "Environmental Hazards" heading: "This product is moderately toxic to aquatic invertebrates and fish. Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when cleaning equipment or disposing of equipment washwaters. Do not allow runoff into lakes, streams, ponds or public waterways."

The non-target insect study was considered to be supplemental because the study did not follow EPA Guidelines and the insects used were Asian insect pests of agricultural crops instead of beneficial insects usually tested. However, the results of the study indicate that polyoxin D zinc salt was not toxic to two-spotted spider mites, diamond back moths and brown plant hoppers at rates up to 400 ppm. This rate represents slightly over 10 times the estimated field application rate. When making a risk determination, the Agency considers the whole body of evidence presented for registration. Therefore, the Agency believes the limited, turf only application sites, and the results of the supplementary non-target insect study, provide enough information to conclude that risks to non-target insects are expected to be minimal.

The registrant was granted data waivers for non-target plants and honeybee toxicity studies based on the limited turf only application sites and expected minimal exposure to pollinating insects, i.e. honeybees.

Table 5. Non-target Toxicity Studies with Polyoxin D Zinc Salt

Guideline No.	Study	Results	MRID
154-6	Avian Acute Oral LD_{50} (Mallard Duck)	> 2150 mg/Kg	432618-40
154-7	Avian Acute Dietary LC_{50} (Mallard Duck)	> 5000 ppm	432618-41
154-8	Freshwater Fish LC_{50} (Rainbow Trout)	96 hr LC_{50}: 5.06 (3.5-10) ppm polyoxin D zinc salt/L; 1.02 (0.73 - 2.1) p.m. polyoxin D/L	432618-42
154-9	Freshwater Invertebrate LC_{50} (*Daphnia magna*)	probit LC_{50} 1.35 (1.12 - 1.78) ppm polyoxin D zinc salt	432618-43
154-10	Non-target Plant Test	data waiver request	waived
154-11	Non-target Insect Test	supplemental	432618-44
154-11	Honeybee Test	data waiver request	waived

2. Environmental Fate and Ground Water Data

The need for environmental fate and ground water data was not triggered under current requirements for the proposed products due to the use pattern, application methods, and mitigation of nontarget aquatic organism toxicity with appropriate precautionary label statements under "Environmental Hazards."

Estimated environmental concentrations were made based on the application rate and usage patterns: estimated concentration from runoff of residues into surrounding aquatic habitats from a 10 acre drainage basin into a 6 foot deep 1 acre pond would be approximately 1.6 ppb per 1% residue runoff. However, any effects from runoff residues in aquatic environments will be mitigated through the label language triggered by the aquatic non-target toxicity studies.

Estimated environmental concentrations are expected to reach maximum residue levels of from 9 ppm to 62 ppm for foliar surfaces of most plant types. These levels are expected to pose minimal levels of risk to mammalian and avian wildlife based on present toxicological data.

3. Ecological Exposure and Risk Characterization

a. Exposure and Risk to Non-target Terrestrial Animals

Toxicological studies indicated that there is no significant toxicity to rodents from acute oral testing at the maximum hazard dose. Therefore, risk to mammalian wildlife is expected to be minimal to nonexistent. Based on the results of the non-target insect study, exposure to polyoxin D zinc salt is not expected to pose significant increased risks to terrestrial insects.

b. Exposure and Risk to Aquatic Animals

Exposure to aquatic invertebrates and vertebrates could occur based on current label use directions. Results of submitted aquatic non-target studies indicated polyoxin D zinc salt is moderately toxic to rainbow trout and freshwater invertebrates. However, with the appropriate aquatic mitigating label language, the exposure and therefore risk to aquatic species is expected to be minimal.

c. Exposure and Risk to Non-target Plants

Exposure to non-target plants is unlikely based on the turf only use pattern and the relatively low application rates, 117 g/A of polyoxin D zinc salt. Furthermore, the mode of action is specific to certain fungi and should not pose risk to other plants.

d. Exposure and Risk to Endangered Species

Threatened or endangered species commonly inhabit undisturbed ecosystems. The end-use product, STOPIT™ Wettable Powder Turf Fungicide is for use only on turf. Turf sites are commonly intensely managed areas and as such are undesirable habitat for threatened or endangered species. Therefore, exposure to threatened or endangered species is considered unlikely. In addition, the low application rate of polyoxin D zinc salt, at 117 g/A, further reduces the possibility of exposure to threatened or endangered species. Therefore, risk to threatened or endangered species from exposure to polyoxin D zinc salt is considered minimal to non-existent.

Polyoxin D Zinc Salt Technical and STOPIT™ Wettable Powder Turf Fungicide pose practically no threat to threatened or endangered species when used according to label directions. Polyoxin D zinc salt was found to be practically non-toxic to the mallard duck, which is a representative species for avian risk assessment. These findings indicate minimal-to-no risk to threatened or endangered birds. The intended use pattern is turf use only and is not intended for use on commercial turf crops.

The ecological risk assessment indicated moderate toxicity to rainbow trout with a 96-hr LC_{50} of approximately 5.06 ppm polyoxin D zinc salt/L for rainbow trout and an EC_{50} of 1.4 mg/polyoxin D zinc salt/L for neonate freshwater invertebrates. In order to mitigate possible risks to aquatic threatened or endangered species, the ecological risk assessment recommended that the end-use product label include the following precautionary language within a statement titled "Environmental Hazards": "This product is moderately toxic to aquatic invertebrates and fish. Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when cleaning equipment or disposing of equipment washwaters. Do not allow runoff into lakes, streams, ponds or public waterways."

IV. Risk Management Decision

A. DETERMINATION OF ELIGIBILITY FOR REGISTRATION

Section 3(c)(5) of FIFRA provides for the registration of new active ingredients if it is determined that (1) its composition is such as to warrant the proposed claims for it; (2) its labeling and other material required to be submitted comply with the requirements of FIFRA; (3) it will perform its intended function without unreasonable adverse effects on the environment; and (4) when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment.

All FIFRA Section 3(c)(5) criteria have been satisfied in the course of the risk characterization. All risk considerations have been adequately addressed and are reflected in the appropriate label language.

Therefore, STOPIT™ Wettable Powder Turf Fungicide and Polyoxin D Zinc Salt Technical are eligible for registration. The proposed uses are turf sites including golf courses, home lawns, parks and commercial and institutional grounds and are listed in Table 4, Appendix A. The uses do not include use on turf being grown 1) for sale or other commercial use as sod, 2) for commercial seed production, or 3) for research purposes.

B. REGULATORY POSITION

1. Conditional/Unconditional Registration

All data requirements are fulfilled and the Biopesticides and Pollution Prevention Division recommends unconditional registration of Polyoxin D Zinc Salt Technical and STOPIT™ Wettable Powder Turf Fungicide.

2. Tolerance Reassessment

There are no food uses pertaining to the registration of polyoxin D zinc salt and therefore are no tolerance issues.

3. CODEX Harmonization

There are no Codex harmonization considerations since there is currently no Codex tolerance for polyoxin D zinc salt residues.

4. Non-food Re/Registrations

There are no non-food use issues at this time. The non-food uses are listed in Table 4, Appendix A.

5. Risk Mitigation

Since there are no risk issues, no risk mitigation measures are required at this time for dietary risk, occupational and residential risk, risks to most non-target organisms (plants and wildlife), or ground and surface water contamination for these products. Both product labels will, however, bear Enviromental Hazards text to mitigate the potential risk to aquatic species.

6. Endangered Species Statement

Currently, the Agency is developing a program (The Endangered Species Protection Program) to identify all pesticides whose use may cause potential adverse impacts on threatened or endangered species and their habitats. To aid in the identification of threatened or endangered species and their habitats, several companies have formed an Endangered Species Task Force (EST) under the direction of the American Crop Protection Association (ACPA). Moreover, the EST will assist in providing species location information at the subcounty level, and particularly if a threatened or endangered species occurs in areas where pesticides would be used. This information will be useful once the Endangered Species Protection Program has been implemented.

Prior to the implementation of the Endangered Species Protection Program, the Agency will not impose specific labeling on those pesticides that pose risks to threatened or endangered species and their habitats but will defer imposing specific labeling language until the implementation of the Program.

C. LABELING RATIONALE

1. Human Health Hazard

a. Worker Protection Standard

This product does not fall under the Worker Protection Standard (WPS), therefore there are no human health hazard labeling issues associated with the WPS.

b. Non-Worker Protection Standard

There are no non-WPS human health hazard issues.

c. Precautionary Labeling

The Agency has examined the toxicological data base for polyoxin D zinc salt and concluded that the following proposed labeling (i.e. Signal Word CAUTION for both Polyoxin D Zinc Salt Technical and STOPIT™ Wettable Powder Turf Fungicide) is appropriate:

For Polyoxin D Zinc Salt Technical, "CAUTION" and "Causes moderate eye irritation. Harmful if absorbed through the skin. Avoid contact with skin, eyes, or clothing. Wash thoroughly with soap and water after handling."

For STOPIT™ Wettable Powder Turf Fungicide, "CAUTION" and "Causes moderate eye irritation. Harmful if absorbed through the skin. Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling."

d. Spray Drift Advisory

A spray drift advisory statement is not needed on the labeling for the proposed uses of Polyoxin D Zinc Salt Technical or STOPIT™ Wettable Powder Turf Fungicide, due to the composition of the end-use product and its domestic, noncommercial use pattern.

2. Environmental Hazards Labeling

Provided the following statements are placed into the Environmental Hazards section, the risk of polyoxin D zinc salt is minimal to nonexistent to non-target organisms, including threatened or endangered species.

a. End-Use Product Environmental Hazards Labeling

"This product is moderately toxic to aquatic invertebrates and fish. Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when cleaning equipment or disposing of equipment washwaters. Do not allow runoff into lakes, streams, ponds or public waterways."

b. Manufacturing-Use Product Environmental Hazards Labeling

"This product is moderately toxic to aquatic invertebrates and fish. Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or other waters unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA."

3. Application Rate

It is the Agency's position that the labeling for the end-use pesticide product containing polyoxin D zinc salt complies with the current pesticide labeling requirements. The Agency has not imposed a maximum number of allowable applications for the active ingredient. However, a maximum quantity of end-use product

per application (four ounces of end-use product, or 0.006 pounds of active ingredient) per 1,000 square feet is specified on the label.

D. LABELING

(1) Product name: **Polyoxin D Zinc Salt Technical**

The signal word is "Caution," based on the submitted acute toxicity study results. A copy of the proposed label is attached.

(2) Product name: **STOPIT™ Wettable Powder Turf Fungicide**

The signal word is "Caution," based on the submitted acute toxicity study results. A copy of the proposed label is attached.

V. Actions Required by Registrants

Reporting of adverse effects to humans or domestic animals under FIFRA, Section 6(a)2 and incidents of hypersensitivity under 40 CFR Part 158.690(c), guideline reference number 152-16 is required.

VI. Appendix A

Table 4 lists the uses sites for each product. The proposed labels for the products are also attached.

TABLE # 4: Nonfood Use Site Registrations

Polyoxin D Zinc Salt Technical Nonfood Use Sites For manufacturing use only for the production of fungicide formulations for use on turf of golf courses, home lawns, parks, and commercial and institutional grounds. **STOPIT™ Wettable Powder Turf Fungicide** Nonfood Use Sites The end-use product, STOPIT™ Wettable Powder Turf Fungicide, is not for use on turf being grown 1) for sale or other commercial use as sod, 2) for commercial seed production, or 3) for research purposes. It is for use on turf on all other turf sites including golf courses, home lawns, parks and commercial and institutional grounds.	Official Date: registered,